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Title: Immunological and virological profile of children with chilblain-like lesions and SARS-CoV-2

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Dear Editor,

The link between SARS-CoV-2 and the reported cutaneous manifestations has not been established. We assessed a possible correlation between the paediatric dermatological manifestations and the biological investigations, using for the first time 3 different SARS-CoV-2 tests.

From April to June, 2020, minors presenting with skin manifestations and symptoms of COVID-19 themselves or any of first-degree relatives (i.e. fever, influenza-like, respiratory, Ear-Nose-Throat and/or digestive symptoms), were enrolled. Epidemiological and clinical information, description of households and biological results including 3 types of SARS-CoV-2 tests [nasal PCR (systemic symptoms within the past 48 hours), serology (IgG, techniques: Abbott ARCHITECT), and interferon-γ(IFN-γ)-ELISPOT-assay] were collected. IFN-γ-ELISPOT-assay, an early (since day 5) qualitative and quantitative analysis, evaluates specific memory T-cells by quantifying the IFN-γ production after a short-term stimulation with SARS-COV-2 peptide. At least one test among serology and IFN-γ-ELISPOT-assay was performed on patients with chilblains.

Thirty patients (20 boys, average = 9.5 years) representing 28 households were included. Thirty-seven symptomatic first-degree relatives were analyzed. In 23/30 patients (77%) and 14/17 (82%) of chilblains patients, COVID-19 was suspected in at least one first-degree relative and confirmed in 4 including 2 with chilblains.

Chilblains were reported in 17 patients with a large spectrum of severity (Figure 1). Lesions occurred before (n=2, average: 19 days), simultaneously (n=2, 12%) or after systemic manifestations (60%, average: 22 days). Spontaneous resolution was complete in an average of 27 days (10-50). Two patients relapsed in 15 and 45 days respectively. Other cutaneous manifestations occurred before (20%, average: 18 days), during (30%) or after systemic manifestations (50%, average: 25 days). Two patients, including 1 child, presented with a linear pattern of urticarial lesions, both also presented with chilblains (Figure 1).

Elevated CRP [average 14mg/L (0 to 200)] and/or increased inflammatory cytokines were noted in 11 children (37%) including 8/17 with chilblains (47%). Cytokine levels were increased in 58%, 50%, 40% and 33% of chilblains patients tested for: TNF-α (range 20-60pg/ml), IL-1 (range 7-280pg/ml), type 1 IFN (range 2-6UI/ml) and IL-6 (range 10-127pg/ml) respectively (Table 1). In chilblains, tests were performed in an average of 18 days (5-98) and 21 days (6-51) after skin lesions and systemic manifestations onset respectively.

The 3/3 nasal PCR were negative. Serology was positive in only 1/16 chilblains patient among the 26 patients tested. IFN-γ-ELISPOT-assay was negative in all the 10 chilblains patients tested. In children with chilblains, these tests were performed in an average of 45 days from lesions onset (5-82) and 56 days from systemic manifestations (35-89).

High levels of cytokines, mostly TNF-α, IL-1, type 1 IFN and IL-6 were noted in 47% of chilblains patients. Biological inflammation was not correlated with: 1/ time lapses from cutaneous or systemic symptoms to the blood test, 2/ severity of chilblains. A cytokine storm was described in adults with COVID-19 (8) and in the paediatric inflammatory multisystem syndrome temporally associated with SARS-COV-2 infection (PIMS-TS): elevated CRP and IL-6 levels (9).

The peak of incidence of COVID-19 and the reported chilblains occurred simultaneously (1-7). In 28/68 reported patients presenting chilblains (5,7,10), serology was negative. Only 1/16 chilblains children serology was positive. Sensitivity of our technique varies from 100 to 85% in severe or mild symptomatic patients respectively. Moreover it is known to be positive after 19 and 30 days of evolution in 85% and 94% of the patients respectively. In all our patients, the COVID-19 was confirmed only once, using 3 different methods. Our result might reflect the estimated prevalence of seropositivity for SARS-CoV-2 in the general French population.

While epidemiological data, clinical manifestations and elevated cytokines level suggest an association with SARS-CoV-2, no evident link could have been made.

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The patients in this manuscript have given written informed consent to the publication of their case details.

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Legends of the table and figure:

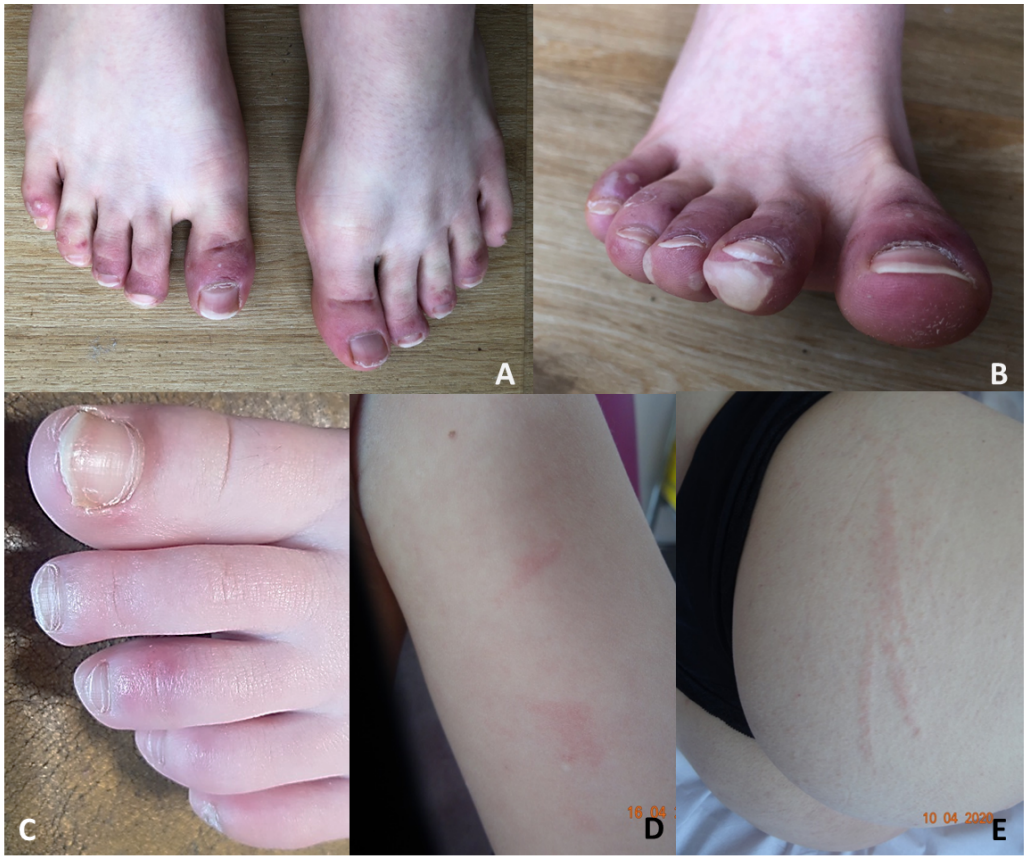
Table 1: Clinical and biological characteristics of the patients

Figure 1: Clinical picture of our paediatric series during the COVID-19 pandemic: chilblain-like lesions associated with livedo (A, B and C), spontaneous urticarial lesions with linear disposition (D and E).

Table 1: Clinical and biological characteristics of the patients

	Total patients, n=30 (%)	**Chilblain-like patients, n=17 (%)**
Mean age (extremes), sex ratio F:H	9.5 y (1.8-17.3), 0.5	11.2 y (1.8-17.3), 0.4
Household contact with a case of COVID-19:		
- Probable cases	23 (77)	14 (82)
- Confirmed cases: PCR / serology / both	2 (7) / 1 (3) / 1 (3)	2 (12) / 0 / 0
Households description:		
- Number of households	28	15
- Total of first degree relatives	79	13
Past medical history of patients:		
- Raynaud phenomenon, photosensitivity	0	0
- Auto-immune disease	0	0
- Inflammatory bowel disease	1 (3)	0
- Asthma / Atopic dermatitis	3 (10) / 2 (7)	3 (19) / 2 (12)
- Urticaria	1 (3)	1 (6)
- Obesity	0	0
Dermatological manifestations:		
- Chilblains: total / feet / hands /both	17 (57) / 14 (47) / 2 (7) / 1(3)	17 (100) / 14 (82) / 2 (12) / 1 (6)
- Eccrine hidradenitis	2 (7)	-
- Maculo-papular rash	8 (27)	-
- Urticaria	1 (3)	-
- Livedo	2 (7)	-
- Targetoid lesions	2 (7)	-
- Vascular / ecchymotic purpure	1 (3) / 1 (3)	-
- Erythema nodosum	1 (3)	-
- Mucosal manifestations	0	-
Average time of cutaneous complete remission	22 d (1-50)	27 d (10-50)
Symptoms:		
- Mean pruritus scale from 1 to 10	7 (1-10), n=11 (33)	6 (1-10), n=6 (62)
- Mean VAS pain scale from 1 to 10	6 (2-10), n=9 (27)	5 (3-8), n=4 (50)
Systemic manifestations:	**n=20 (67)**	**n=10 (59)**
- Fever	10 (33)	3 (18)
- Influenza-like symptoms	13 (43)	7 (41)
- Respiratory symptoms	10 (33)	6 (35)
- ENT symptoms **/** anosmia	10 (33) / 1 (3)	7 (41) / 0
- Digestive symptoms	7 (23)	3 (18)

- Articular symptoms	1 (3)	0
Mean time lapse from systemic symptoms to lesions:	**n=20 (67)**	**n=10 (59)**
- Systemic manifestations before	25 d (3-77), n=10 (50)	22 d (5-46), n=6 (60)
- Cutaneous manifestations before	18 d (2-30), n=4 (20)	19 d, n=2 (20)
- Simultaneous manifestations	0 d, n=6 (30)	0 d, n=2 (20)
Laboratory tests:	**n=25 (80)**	**n=16 (94)**
- Anemia (Hb<11g/dl)	1 (4)	0
- Hyperlymphocytosis (>5,2G/l)	2 (8)	0
- Neutrophilic hyperleukocytosis (>8G/l)	1 (4)	1 (6)
- Elevated liver enzymes (ALT, AST)	0	0
- Elevated creatinine	1 (4)	0
- Elevated CRP (>5mg/l), mean (extremes)	3 (12), 14 (0-200)	1 (6), 5 (0-49)
- Low PT (<70%)	2 (8)	1 (6)
- Elevated aPTT (ratio>1,2)	6 (24)	3 (19)
- Elevated fibrinogène (>3,5g/l) (n=15)	0	0
- Elevated D-dimer level (>500ng/ml) (n=15)	1 (7)	0
- Positive antinuclear antibodies, mean title (extremes), specificity (n=17)	14/17 (82), 264 (100-800), 0	11/14 (79), 263 (100-800), 0
- APLA syndrome (β2GP1, cardiolipin, lupus anticoagulant) (n=15)	1/15 (7)	1/12 (8)
- Positive C-ANCA, specificity (n=17)	4/17 (23), 0	2/14 (14), 0
- Complement anomalies: C3, C4, CH50 (n=9)	1 low CH50 at 66 (4)	1 low CH50 at 66 (7)
- Elevated cytokines serum concentrations:		
○ IL1 (> 15pg/ml), mean (range)	6/14 (43), 105 (17-280)	6/12 (50), 104 (7-280)
○ IL6 (>10pg/ml), mean (range)	5/15 (33), 59 (10-127)	4/12 (33), 62 (10-127)
○ TNF-α (> 20pg/ml), mean (range)	7/15 (47), 33 (20-60)	7/12 (58), 31 (20-60)
○ Type 1 IFN (α) (> 2UI/ml), mean (range)	4/12 (33), 4 (2-6)	4/10 (40), 4 (2-6)
Tests of SARS-CoV-2:		
- **PCR positive**	0/8	0/3
- **IgG positive (Abbott ARCHITECT)**	1/26 (4)	1/16 (6)
- **ELISPOT**	11/11 (100)	10/10 (100)
Mean duration of follow-up	34 d (8-72)	42 d (11-72)



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